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The Role of Neo-Sinus Reconstruction In Aortic Valve Sparing Surgery

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Abstract

Aims. The aim of this study was to evaluate the clinical and echocardiographic results and the predictors of outcomes in patients undergoing valve sparing operation (VSO) at two aortic centers. In addition, we sought to evaluate the potential effect of recreation of the sinuses of Valsalva (SV) on the outcome of valve sparing procedures.

Methods. During a 14-year period 328 patients underwent aortic valve sparing root replacement at two Institutions. Clinical and echo evaluation was performed 6 months after surgery and every year thereafter or in case of clinical symptoms. Propensity weighting and propensity-weighted risk competing analysis were used.

Results. No operative mortality was reported; the most common complication was revision for bleeding, occurring in 15 patients (4.6%). At a mean follow-up of 30.0 ± 33.9 months, 2 patients died (0.6%). Recurrent aortic insufficiency (AI) $>2+$ was found in 11 patients (3.3%); 5 (1.5%) underwent reoperation. Recreation of the SV did not affect clinical outcome and aortic valve status. Need for aortic valve repair was the only independent predictor of recurrent AI, whereas a bicuspid aortic valve was a protective factor.

Conclusions. Re-creation of the SV does not affect short-term outcomes following VSO.

Keywords: Valve sparing aortic surgery; Valsalva sinuses; David procedure.

Preservation of the patient's native aortic valve offers substantial advantages over aortic valve replacement, avoiding potential prostheses-related complications and the need for long-term anticoagulation¹. Nevertheless, aortic valve sparing operation (VSO) may be technically challenging: significant experience is required not only to perform the procedure but also to select the appropriate patients and valve pathology in order to obtain favorable results.

The importance of the recreation of the sinuses of Valsalva (SV) during aortic VSO remains a matter of controversy. Despite solid experimental and in vivo evidence of the physiologic importance of the SV for aortic valve function^{2,3}, there is limited data comparing the outcome of patients undergoing VSO with and without SV reconstruction.

We present the clinical and echocardiographic results of 328 patients undergoing aortic VSO at two centers and compare the outcomes of patients with and without neo-SV.

Methods

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by both the institutions' human research committee. The need for individual patient consent was waived.

Review of prospectively collected data from the aortic surgery databases of the Weill Cornell Medical College Department of Cardiothoracic Surgery in New York and the Department of Cardiac Surgery of the European Hospital in Rome was conducted to identify all consecutive patients who underwent VSO from September 2002 to November 2015.

Primary end-points were operative mortality, all cause death at follow-up, reoperation on the aortic valve and echocardiographic evidence of recurrent aortic insufficiency (AI) >2+ at follow-up. Secondary endpoints were the incidence of major postoperative complications (myocardial infarction, cerebrovascular accident with permanent deficit, respiratory failure leading to tracheostomy, acute renal insufficiency requiring dialysis, deep sternal wound infection) and a composite index of major postoperative adverse events (MAE: operative death and major postoperative complications).

Surgical treatment was indicated by valvular and aortic pathologic criteria according to the established best-practice, ESC/EACTS⁴ and AHA/ACC⁵ guidelines. Details of the surgical techniques used in the two centers have been previously published^{6,7}.

All operations were performed using median sternotomy, central cannulation, moderate hypothermic cardiopulmonary bypass, aortic cross-clamping and myocardial protection with cold antegrade blood cardioplegia. In both centers the classical David 1 technique was used⁸. At Weill Cornell Medical College, a straight Dacron tube without SV was always employed (Macquet Corp, Fairfield, NJ, USA), whereas at the European Hospital a graft with neo-SV was used for all cases (Vascutek[®] Gelweave Valsalva[™] Grafts, Terumo, Inchinnan, Scotland, United Kingdom).

The databases of both Institutions are constantly updated and maintained by a team of clinical information analysts; data collection is validated regularly by means of external and internal control. Pre- and perioperative variables are entered prospectively during in-hospital stay. Postoperatively, follow-up clinical and transthoracic echo evaluation is performed at 6 months after surgery and every year thereafter or in case of clinical symptoms suggestive of aortic disease. Aortic regurgitation is assessed by color-flow Doppler techniques in the standard transthoracic views and graded according to the current guidelines⁹. In case of missing/unreliable data direct interview with the patient, a relative or the treating physician is performed.

Statistical Analyses

Continuous variables were summarized statistically with standard deviations in addition to means and with counts in addition to percentages for categorical variables. The chi squared test was used to test unadjusted association between treatment variable and outcomes.

For intergroup comparison, crude incidences of outcomes were reported in the whole sample according to the type of graft used (graft with neo-SV versus graft without neo-SV). In order to assess the effect of graft selection on the incidence of postoperative recurrent aortic regurgitation and need for reintervention we conducted a propensity score based analysis on patients who underwent surgery for chronic aneurysm only. Inverse probability of treatment weighting for modelling causal effects was used for treatment effects comparison. A generalised boosted model was implemented to estimate logistic propensity scores (PS) adjusting for pre-treatment covariates including the morphology of the aortic valve and the preoperative degree of AI, and the propensity score was assumed as the probability that an individual of the Valsalva group receives the straight tube graft (twang R package). The average treatment effect on the treated was used to answer the question of how, on average, the outcome of interest would change if everyone assigned to a particular treatment would have received another treatment. The absolute standardised mean difference was used as a balance metric to summarize the difference between two univariate distributions of a single

pre-treatment variable. A value ≥ 0.20 (20%) was considered as an indicator of imbalance. Effective sample size was calculated to account for the potential loss in precision from weighting¹⁰. We then estimated the treatment effect estimates with a weighted competing risk analysis regression model that contained only a treatment indicator¹¹. R version 3.1.2 (2014-10-31), twang and cmprsk packages were used for all statistical analysis.

Results

During the study period 328 patients underwent VSO at the two Institutions (227 at Weill Cornell Medical College and 101 at the European Hospital). The main pre- and intraoperative characteristics of these patients are summarized in Table 1.

The majority of the patients were males in their fifth decade and in New York Heart Association (NYHA) class 1 or 2, and 20% of them had connective tissue disorders.

No operative mortality was reported in both centers. The type and incidence of postoperative complications are summarized in Table 2. Re-exploration for bleeding was the most common postoperative adverse event (15 cases, 4.6%). Dialysis-requiring new onset renal insufficiency occurred in two cases (0.6%) and postoperative myocardial infarction in one case (0.3%). The overall incidence of MAE was 0.9%. At discharge, no patients had echocardiographic evidence of AI >1+.

Mean follow-up duration for the overall population was 30.0 ± 33.9 months (mean follow-up of patients receiving neo-SV versus those not receiving neo-SV: 54.5 ± 42.1 versus 19.1 ± 22.2 months, respectively). Completeness of follow-up was 100%. During this period, two patients died (overall mortality: 0.6%) (Figure 1) and 11 patients (5.6%) developed AI >2+ (Table 3, Figure 2B). Five of these patients (1.5% of the total) required reoperation on the aortic valve (Table 3, Figure 2A). All cases of reoperations were due to structural valve deterioration.

No difference in operative outcome was found between the two unweighted groups (Tab 2 and 3). During follow-up 1 patient from each group died ($p=.55$). The Kaplan-Meier survival curves of the two unweighted groups are reported in Figure 1. There were three cases of reoperation in the neo-SV graft group and 2 in the group of patients receiving a graft without neo-SV ($p=.86$). Six patients in the neo-SV group and 5 in the group without neo-SV developed recurrent AI >2+ ($p=.28$).

A total of 97 patients receiving a neo-SV graft and 220 receiving a graft without neo-SV for chronic aortic aneurysm were included in a propensity based analysis. After PS weighting the two groups were comparable for all pre-treatment variables (Supplementary Table 1 and Supplementary Figure 1).

PS-weighted risk competing analysis showed that the two groups presented similar short-term mortality and incidence of reoperation (Figure 3A). The neo-SV graft group and the group of patients receiving a graft without neo-SV also presented a comparable incidence of AI >2+ at follow-up (Figure 3B). By performing a full adjustment, we found that the need for aortic valve repair was the only independent predictor of follow-up AI >2+, whereas bicuspid aortic valve was a protective factor ($p < .0001$ for both).

Discussion

The term “aortic VSO” was introduced in the early 1990s in order to define those procedures in which aortic valve cusps were preserved in patients with aortic root/ascending aorta aneurysm. Two different techniques were first described¹²: the “remodeling” technique (or “Yacoub” technique)¹³ which reduces the sinotubular junction diameter and creates three neo-SV with a scalloped Dacron tube graft sutured in the supra-ventricular position, and the “reimplantation” technique (or “David” technique)⁸, by which the aortic valve is resuspended into a straight prosthetic tube.

Preservation of the patient’s native aortic valve in case of aortic root surgery offers substantial advantages over aortic valve replacement. Avoidance of the need for long-term anticoagulation and potential mechanical prostheses-related complication, as well as low durability and rapid degeneration in case of biological prostheses are strong arguments in favor of VSO over traditional surgery. Price et al. evaluated long-term outcomes of aortic root operations in 165 patients with Marfan syndrome who underwent a Bentall or VSO. While late survival, freedom from root reoperation, and freedom from endocarditis were similar in the two groups, VSO resulted in significantly fewer thromboembolic and hemorrhagic events (hazard ratio, 0.16; 95% confidence interval, 0.03-0.85; $p = .03$)¹⁴. In a prospective multicenter study, Coselli and colleagues compared 1-year results after aortic VSO or aortic valve replacement in 316 patients with Marfan syndrome¹⁵. Survival was similar between the 2 groups but AI $>2+$ at follow-up was present in 16 patients in the VSO group (7%) versus no patients in the valve replacement group ($p = .02$). Long-term outcomes following 4 different types of aortic root procedures combined with ascending aorta replacement for aneurysm in 957 patients were studied by Svensson et al¹⁶. At 10 years, patients in the VSO and allograft groups were more likely to show severe AI (24% and 19%, respectively; $p = .2$) when compared to those who received a biologic or a mechanical composite graft (2.7% and 0%, respectively). Patients who underwent composite graft replacement with a biologic valve had the worst survival ($p < .0001$), mainly attributable to differences in patients’ characteristics. VSO and allograft procedures had the lowest gradients and best ventricular remodeling as well as less risk of valve-related complications, such as bleeding, hemorrhage, and endocarditis.

An important issue regarding VSO is whether concomitant aortic cusp repair may influence valve function over time. Consistent with previous findings from other groups¹⁷, we found that the need for aortic valve repair was an independent predictor of AI at follow-up. Although several factors may play a role in this context, we believe that secondary fibrotic retraction of the cusp margins after interventions may be critical in this regard.

Our findings on the protective effect of bicuspid aortic valves, although counterintuitive at first, is probably explained by a selection bias. It is likely that the operating surgeons had an instinctively higher threshold for VSO in case of bicuspid valves and thus selected only the best valves for VSO. Our findings confirm that bicuspid valves may be safely spared during VSO, as reported by others^{18,19}. However, a longer follow-up period will be necessary to determine whether reimplantation of BAVs during VSO will result in less freedom from reoperation due to structural deterioration of the BAV.

In case of VSO, the use of tube graft with neo-SV, mimicking the native structure and dynamics, should theoretically be able to affect valve durability since perturbations of the regular movements of opening and closure of the native aortic valve and alterations in flow dynamics may be avoided²⁰. SV were also demonstrated to have a key role in optimizing the aortic haemodynamics during systole, minimizing energy losses². In addition, Welter and colleagues using finite element computer-assisted stress analysis were able to show that the use of a standard tubular graft can be linked to higher stress to coronary sutures, while using a graft with preformed SV could relieve stress on the coronary anastomoses, potentially decreasing the incidence of postoperative complications such as bleeding and late pseudoaneurysm formation³. However, the clinical impact of these physiological considerations has not been well determined and, consequently, the importance of the recreation of the SV at the time of VSO remains a matter of controversy. Recently the Toronto group reported its 20-year experience with VSO²¹. The authors used a straight tube graft in 216 patients and a tube with neo-SV in 117. On univariate analysis recreation of the SV was associated with the development of moderate or severe AI during follow-up (HR 1.87, 95%CI 1.03-3.42, $p=.04$). However, this was not confirmed on multivariate analysis. Of note, no attempt to match the clinical

or valvular characteristics of patients of the two groups was performed. Our study revealed that short-term outcomes are independent from neo-SV re-creation. The clinical outcome, the incidence of recurrent AI >2+ and of reoperation on the aortic valve were in fact similar in the group with and without neo-VS (see Figures 1-3). It must also be noted that a trend toward better freedom from AI and reoperation in the Non Neo-SV series was evident in our series. Although this difference did not reach statistical significance, this observation requires further investigation in a larger sample size.

Some limitations of our study should be acknowledged. Due to the extremely low rate of adverse events, it is not possible to exclude that small differences in favor of one of the other technique could have been undetected. Also, this study is limited to short-term data, a longer follow-up is needed. The fact that the two study Institutions exclusively adopted one of the two techniques and that the two groups of patients are from different countries may have also influenced the outcomes. Finally, although PSM analysis was performed, it cannot substitute for a randomized controlled study.

In conclusion, the results of VSO are excellent. Recreation of the VS during aortic VSO does not affect clinical outcome and aortic valve status. Additional multi-institutional studies with long term follow-up will be necessary to confirm our findings.

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Table 1. Preoperative characteristics and intraoperative data.

	Overall	Neo-SV	No Neo-SV	p
	(n=328)	(n=101)	(n=227)	
Age (mean, std. dev.)	49.9 ±13.9	52.8 ±12.8	48.6 ±14.2	.013
Male	273 (83.2)	85 (84.2)	188 (82.8)	.764
Chronic pulmonary disease	3 (0.9)	2 (2.0)	1 (0.4)	.176
Diabetes	5 (1.5)	2 (2.0)	3 (1.3)	.653
Previous cardiac surgery	9 (2.7)	1 (1.0)	8 (3.5)	.195
Connective tissue disorder	63 (19.2)	15 (14.9)	48 (21.1)	.182
Aortic dissection				
Acute	11 (3.4)	4 (4.0)	7 (3.1)	.378
Chronic	4 (1.2)	0 (0.0)	4 (1.8)	
NYHA >2	24 (7.3)	7 (6.9)	17 (7.5)	.858
Ejection Fraction <0.45	15 (4.6)	1 (1.0)	14 (6.2)	.038
Renal Status				
Creatinine > 1.5 mg/dL	7 (2.1)	5 (5.2)	2 (0.9)	.033
Hemodialysis	3 (0.9)	0 (0.0)	3 (1.3)	.246
Bicuspid Valve	64 (19.5)	14 (13.9)	50 (22.0)	.085
Aortic Insufficiency				

0-2+	229 (69.8)	69 (68.3)	160 (70.5)	.693
>2+	99 (30.2)	32 (31.7)	67 (29.5)	
Circulatory arrest	26 (7.9)	5 (5.0)	21 (9.3)	.183
Crossclamp time (min)	111.4 ±21.7	104.7 ±18.9	114.4 ±22.2	<.001
Concomitant procedures	96 (29.3)	27 (26.7)	69 (30.4)	.501
Aortic Valve Repair	25 (7.6)	8 (7.9)	17 (7.5)	.892

Data presented as n (%), unless otherwise noted. Mean data is ± standard deviation

NYHA, New York Heart Association; SV, sinuses of Valsalva.

Table 2. In hospital outcome in the unweighted sample.

	Overall	Neo-SV	No Neo-SV	p
	(n=328)	(n=101)	(n=227)	
Operative death	0 (0.0)	0 (0.0)	0 (0.0)	NS
Myocardial infarction	1 (0.3)	1 (1.0)	0 (0.0)	.133
New need for dialysis	2 (0.6)	0 (0.0)	2 (0.9)	.344
Gastrointestinal complications	3 (0.9)	0 (0.0)	3 (1.3)	.246
Revision for bleeding	15 (4.6)	6 (5.9)	9 (4.0)	.429

Data presented as n (%), unless otherwise noted

*Defined as postop creatinine >2 mg/dl

SV, sinuses of Valsalva.

Table 3. Follow-up data in the unweighted sample.

	Overall	Neo-SV	No Neo-SV	p
	(n=328)	(n=101)	(n=227)	
Follow-up death	2 (0.6)	1 (1.0)	1 (0.4)	.555
Aortic Insufficiency				
0-2+	186 (94.4)*	86 (93.5)*	100 (95.2)*	.930*
>2+	11 (5.6)*	6 (6.5)*	5 (4.8)*	
Reoperation on the aortic valve	5 (1.5)	3 (3.0)	2 (0.9)	.154

Data presented as n (%), unless otherwise noted.

*Percentages and p value were calculated based on the total number of patients for whom the echo follow-up was available (n=197 in the overall population; n=92 in the Neo-SV group; n=105 in the No Neo-SV group)

SV, sinuses of Valsalva.

1 **Figure legend**

2 **Figure 1.** Kaplan-Meier survival curves of the overall sample and the two unweighted groups.

3 **Figures 2A and 2B.** Cumulative incidence of reoperation on the aortic valve and cumulative incidence of
4 postoperative aortic insufficiency >2+ at follow-up of the two unweighted groups.

5 **Figures 3A and 3B.** Short-term mortality, incidence of reoperation and incidence of aortic insufficiency
6 >2+ at follow-up of the two PS-weighted groups.

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